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(54) Title: A NOVEL AND IMPROVED PROCESS FRO THE PREPARATION OF NATEGLINIDE AND ITS POLYMORPH FORM-H

(57) Abstract: Nateglinide is prepared by an improved process comprising reaction of trans-4-isopropyl cyclohexane carbonyl chloride with N,O-bis- trimethylsilyl protected D-phenyl alanine to give after aqueous workup, crude nateglinide which is converted to Nateglinide form- H using a mixture of cyclohexane / ethyl acetate. trans-4-isopropyl cyclohexane carbonyl chloride is prepared from trans-4- isopropyl cyclohexane carboxylic acid using oxalyl chloride.

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BACKGROUND OF THE INVENTION :

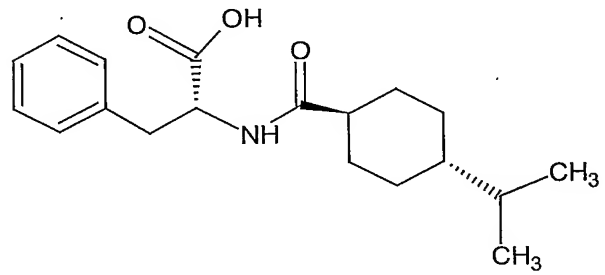
Nateglinide is a derivative of unnatural amino acid D-Phenyl alanine .It is taken immediately before meal and acts directly on pancreatic β-cells to restore the physiological early phase insulin secretion pattern, immediately after meals onset, which is lost in people with type-2 diabetes. It also enhances insulin secretion after meals during periods of elevated glucose levels (Hyperglycemia).

Nateglinide is chemically known as N-[[*trans*-4-(1-Methylethyl)cyclohexyl]carbonyl]-D-phenylalanine

Or

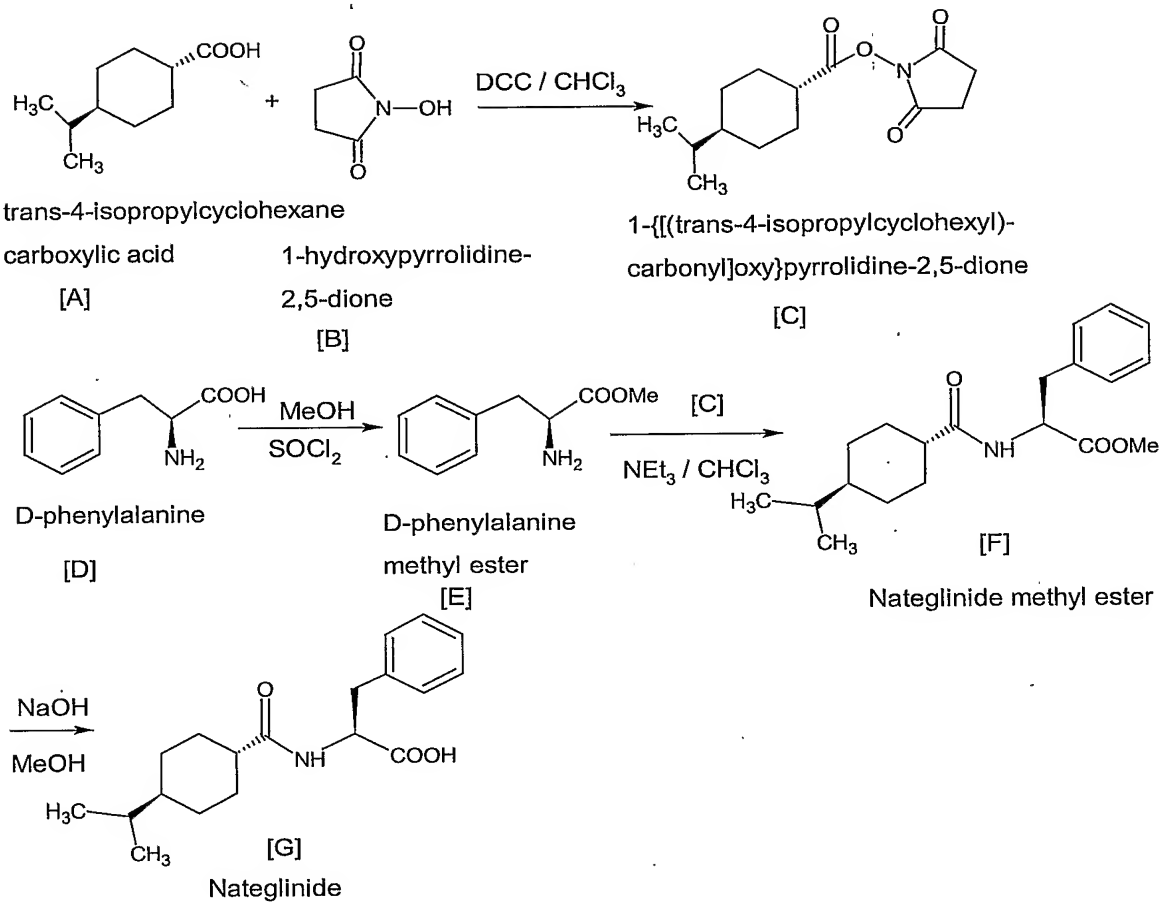
(-)-N-(*trans*-4-isopropylcyclohexyl-1-carbonyl)-D-phenylalanine

Nateglinide has CAS Registry Number [105816-04-4] and is represented by a compound of formula-1



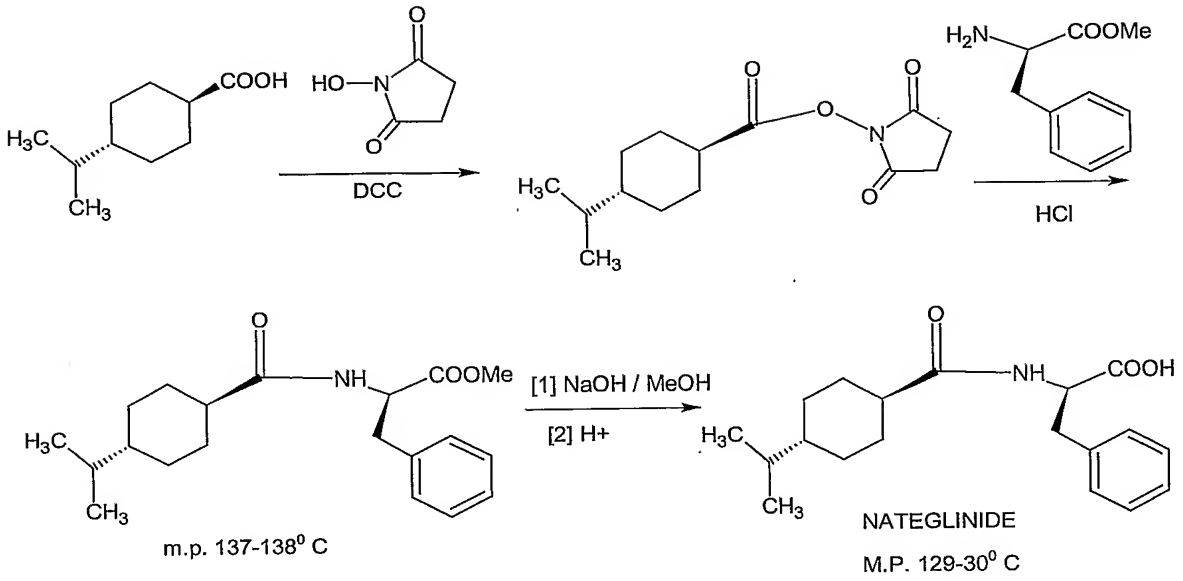
Formula-1

European patent 0196222 (1986) & J. Med. Chem (1989) vol. 32 page 1436 discloses synthesis of Nateglinide from trans 4-isopropyl cyclohexane carboxylic acid as shown in Scheme-1 as follows:



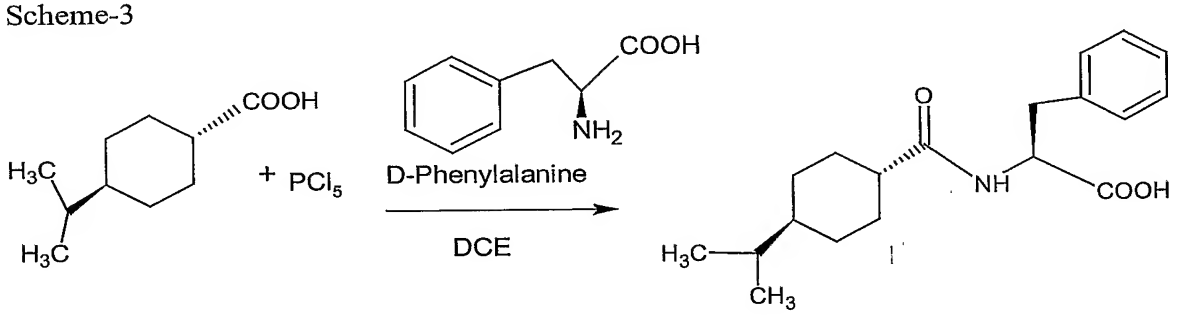
US 4816484 and its subsequent reissue US RE 34878 discloses preparation of Nateglinide as per Scheme-2 as follows:

Scheme-2



JP 7017899 [Equivalent to JP4008794] discloses preparation of Nateglinide from trans isopropyl cyclohexyl carboxylic acid in a single step using PCl_5 as per Scheme-3 :

Scheme-3

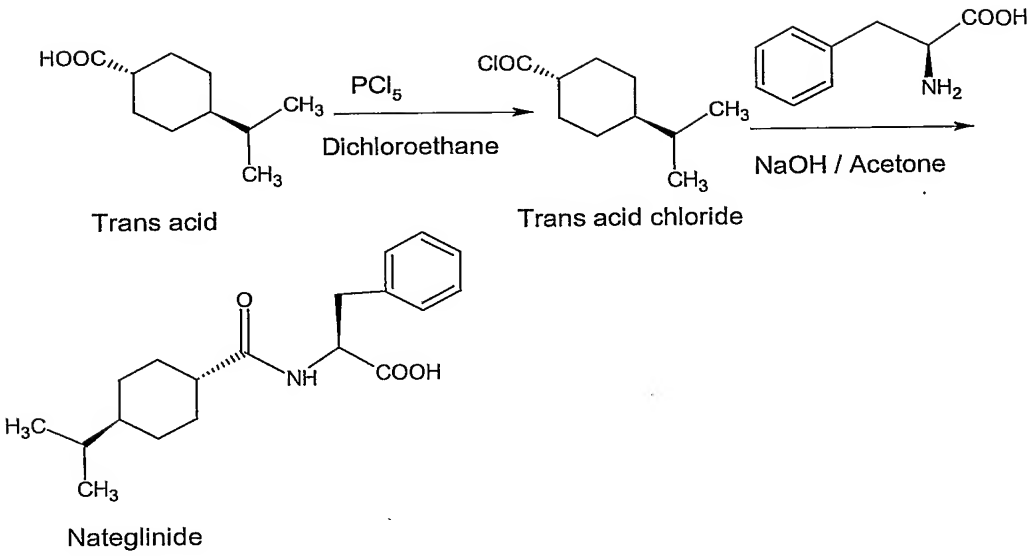


trans-4-isopropyl cyclohexane carboxylic acid

Nateglinide

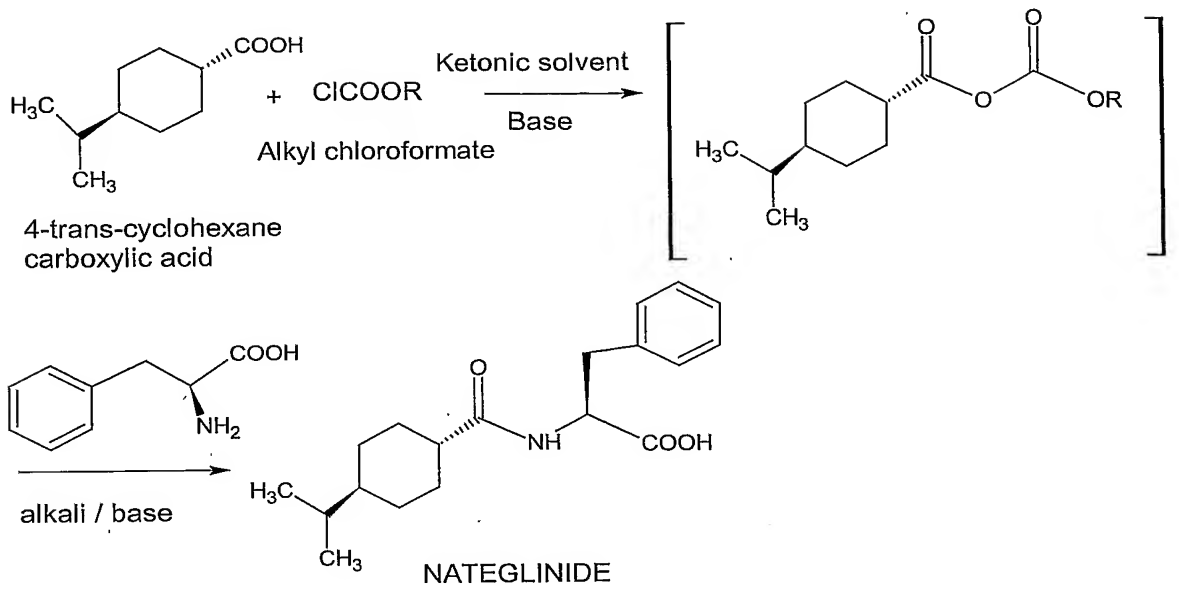
US 4816484, US RE 34878 and EP 196222 also describe other process for the preparation of Nateglinide in which trans-4-isopropycyclohexyl carboxylic acid is converted to its acid chloride and reacted with D-Phenylalanine in acetone using 10% sodium hydroxide to provide Nateglinide as described in scheme-4 :

Scheme-4



WO 2004/018408 discloses a synthesis of Nateglinide in which trans4-isopropyl cyclohexane carboxylic acid is converted to a mixed anhydride using alkyl chloroformate in ketonic solvent and reacting further with D-Phenylalanine in presence of alkali/base to give Nateglinide, these steps are depicted in Scheme-5:

Scheme-5



The drawbacks of this process are low overall yield [44 %] , too many purifications, and use of mixtures of solvents making the process less attractive for commercial production.

WO03/093222 describes the preparation of crystalline form "C" of N-(trans-4-isopropyl cyclohexylcarbonyl)- D- phenylalanine by reacting D-Phenylalanine methyl ester HCl with trans-4-isopropyl cyclohexane carboxylic acid in presence of propane phosphonic acid anhydride or $LiOH\text{-}Al_2O_3$ in halogenated hydrocarbon solvents such as dichloromethane, dichloroethane at a temperature between -10^0C to 90^0C followed by base hydrolysis.

Alternatively, the product can be obtained by reacting *trans*-4 isopropyl cyclohexane carbonyl chloride with D-phenylalanine methyl ester HCl in halogenated hydrocarbon solvents such as dichloromethane, dichloroethane, in presence of base such as triethyl amine, pyridine at a temperature between -10^0C to 90^0C followed by base hydrolysis.

WO 02/32854A1 [equivalent to US 20040030182, EP1334963, CN1481356] describes a process wherein trans-4-isopropyl cyclohexyl carbonyl chloride is reacted with D-Phenylalanine in a mixed solvent of a ketone solvent and water in the presence of an alkali and then adjusting the temperature of the mixture to 58^0C to 72^0C and the concentration ketone solvent to more than 8 wt % and less than 22 wt % to conduct precipitation of Nateglinide crystals.

WO 02/32853A1 [equivalent to US20040024219,EP 1334962, CN 1481355, CA 2425533] describes a process for the preparation of Nateglinide, which comprises the

step of reacting trans-4-isopropyl cyclohexyl carbonyl chloride with D-Phenylalanine in a mixed solvent consisting of an organic solvent and water by keeping the different ratio of organic solvent and water, under conditions kept alkaline with potassium hydroxide.
WO2004/005240A1 provides a process for the preparation of an intermediate in the synthesis of Nateglinide wherein *trans*-4- isopropylcyclohexane acid chloride is formed by reacting 4- isopropylcyclohexane carboxylic acid with thionyl chloride in the presence of an effective amount of an organic amide. It also provides processes for preparation of Nateglinide by acylation of a suitable salt of D-phenylalanine with *trans*- 4-isopropylcyclohexane acid chloride in both a single and a two-phase system, and in water free of a cosolvent.
US 2004/0077725A1 describes a process where in trans-4-isopropyl cyclohexyl carbonyl chloride is reacted with D-Phenylalanine methyl ester hydrochloride in presence of triethylamine in chloroform at room temperature for 10 hours to get a methyl ester of Nateglinide which on base hydrolysis in isopropyl alcohol yields Nateglinide.

In addition to the above references, nateglinide is also discussed in US patents 5463116 and 5488150 which describe the preparation of form H type crystals of Nateglinide by treating B-type nateglinide crystals (obtained by following Ex-3 of Japanese patent application laid open No. 63-54321) with a solvent at a temperature of atleast 10^0C and forming crystals in the solvent at a temperatureof atleast 10^0C.
In general processes described in the prior art ,use hygroscopic, expensive reagents; involve multi-step extractive workup and involve the use of hazardous reagents like PCl5 , DCC, propane phosphonic acid anhydride in ethyl acetate which are not preferred for large scale commercial operations.

SUMMARY OF THE INVENTION :

The main object of the invention is to provide a commercially viable process for the preparation of nateglinide avoiding multistep extraction.

It is another object of the present invention to provide alternate chlorinating agents such as oxalyl chloride for converting trans-4-isopropyl cyclohexane carboxylic acid into trans-4-isopropyl cyclohexane carboxylic acid chloride.

Yet another object of the present invention is to to provide an improved amidating method to give nateglinide comprising reaction of N,O-bis trimethyl silyl protected D-phenyl alanine with trans-4-isopropylcyclohexyl-1-carbonyl chloride in suitable solvent(s) followed by aqueous workup to give nateglinide.

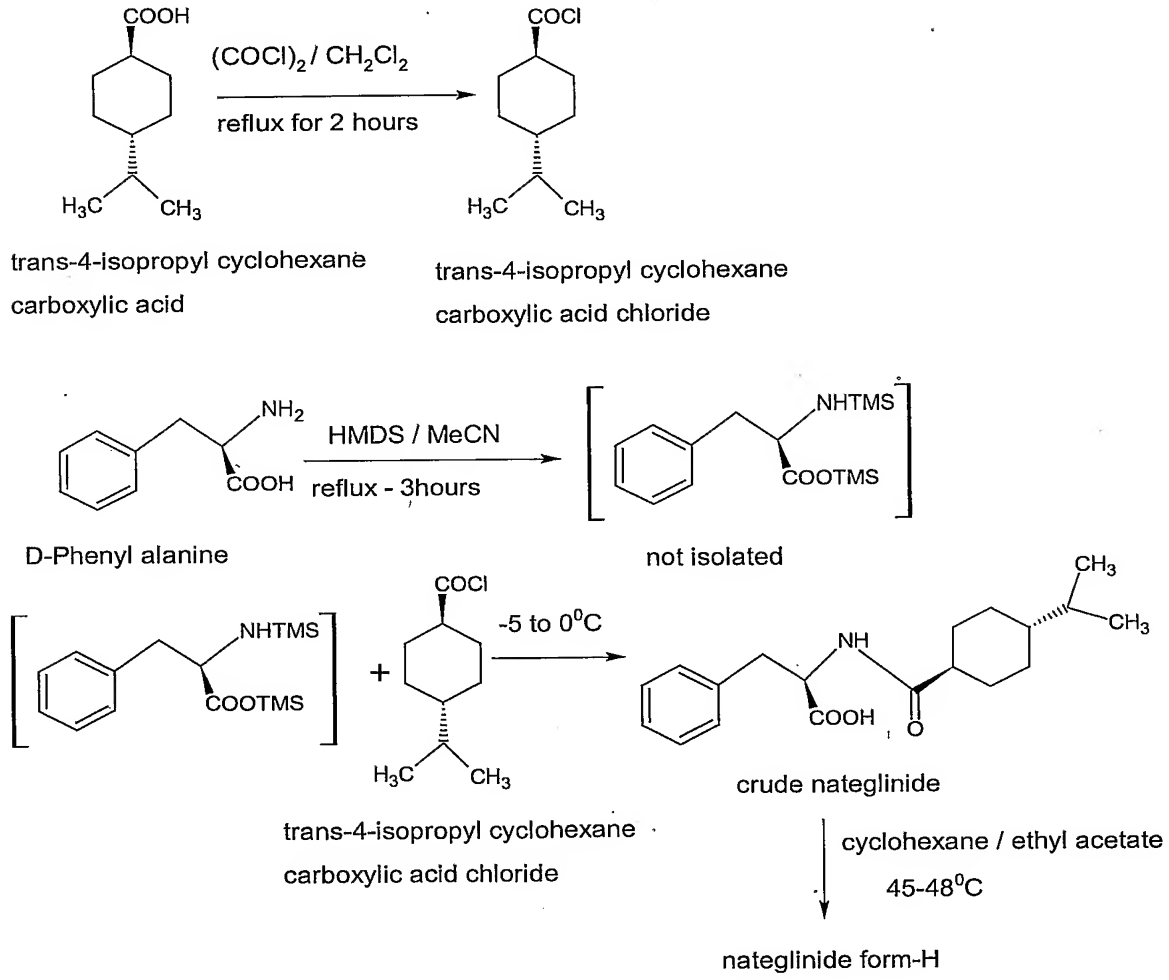
Yet another object of the present invention is to to provide an alternate process for preparation of nateglinide form-H.

DETAILED DESCRIPTION :

The present invention discloses a novel method of synthesis for the preparation of Nateglinide from trans-4-isopropyl cyclohexane carboxylic acid, its conversion to an acid chloride by oxalyl chloride, and subsequent reaction with N,O-bis trimethylsilyl D-Phenylalanine in suitable solvent to give Nateglinide , which is further purified in cyclohexane/ ethyl acetate to give form-H.

The present invention is described as per Scheme-6 as follows :

Scheme-6



Step-a

The chlorinating agent used in this invention is oxalyl chloride.

The solvent for this reaction is selected from:

Aromatic hydrocarbons such as benzene, toluene, xylene or mixtures thereof, paraffins such as hexane , heptane, octane or mixtures thereof, cycloalkanes like cyclohexane, cyclopentane methyl cyclopentane, methyl cyclohexane or mixtures thereof,

halogenated solvents such as dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride or mixtures thereof. The preferred solvent is dichloromethane.
The temperature of the reaction varies from 25°-150°C preferably at the reflux temperature of the solvent.

After the reaction, the solvent (methylene chloride) is distilled under vacuum to yield a product of 98 % purity
Step-b
D-Phenyl alanine is converted into N,O-bis trimethylsilyl D-Phenylalanine by using any of the available reagents like HMDS, BSU, BSA, or other silylating agents, the preferred reagent being HMDS. Solvents for carrying out silylation is selected from:
Aromatic hydrocarbons like Benzene, toluene, xylene or mixtures thereof;
Halogenated solvents like dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride or mixtures thereof;
Ethers like THF, dioxane, 2-Methyl THF, dialkyl ether like diethyl ether,di propyl ether, dibutyl ether , or mixtures thereof;
Paraffins like hexane , heptane, octane or or mixtures thereof;
Cycloalkanes like cyclohexane, cyclopentane , methyl cyclopentane, methyl cyclohexane or mixtures thereof;
Nitrile group of solvents like acetonitrile, propionitrile , or mixtures thereof.
Out of all the most preferred is by using HMDS in acetonitrile as solvent.

The silylation reaction is quantitative Moreover the deprotection of silylated compounds is also very facile and generates products, which are easily removed during workup procedure. The conversion of D-Phenylalanine to N,O-bis trimethylsilyl D-Phenylalanine is carried out at 25^0C to 150^0C, preferably the reflux temperature of the solvent selected.
Silylation of D-Phenylalanine is carried out in solvent (Acetonitrile) using silylating agent (HMDS) at about reflux temperature for about 3 hrs. The reaction mass is then cooled to –5°C to 0°C.
Step-c
A solution of trans-4-isopropyl cyclohexane carboxylic acid chloride in solvent (Acetonitrile) is added to a solution of N,O-bis trimethylsilyl D-Phenylalanine in solvent (acetonitrile) over a period of 35 to 40 minutes maintaining temperature –4° to 0°C. The reaction is further stirred at –4° to 0°C for 3 hours and quenched with ice water, stirred for one hour, filtered , washed with water and dried to give crude nateglinide in 88 to 90% yield with a melting point of 124-128^{0}C and an HPLC purity of 98.5-99.5%

Step-d
Nateglinide prepared in step-2 is further processed using cyclohexane-Ethyl acetate to give Nateglinide form – H crystals.
The process for preparing nateglinide form H is as follows.
Nateglinide is stirred at reflux in cyclohexane and ethyl acetate is added till reaction mixture becomes clear. Then the solution is cooled to 45-48^{0}C and stirred at same temperature for 16 to 18 hours. The reaction mass is cooled to 35 to 40^{0}C , filtered and

washed with cyclohexane and dried at 80-85^{0}C to give Nateglinide form –H with an yield of 81 to 85 % ; melting point of 134-139^{0}C and HPLC purity of >99.7 %
The present invention is illustrated by following examples which do not limit the scope of invention.

Example-1

Preparation of Trans-4-isopropyl cyclohexane carbonyl chloride
In 500 ml multinecked round bottom flask equipped with stirrer, thermometer and reflux condenser were charged 165 ml of methylene chloride and 65 gms of trans –4-isopropyl cyclohexane carboxylic acid and stirred at room temperature. To it was charged 55.3 gms of oxalyl chloride dropwise over a period of 20-25 minutes. The reaction mass was then heated to reflux and maintained at reflux temperature for 1.5 to 2 hours. Methylene chloride was distilled off to give product.
Yield=70 gms
Purity by GC= 98-99%

Example-2

Preparation of crude Nateglinide
In one litre capacity four necked flask equipped with oil bath for heating, stirrer, thermometer, condenser, and nitrogen gas passing arrangement , was charged 250 ml of acetonitrile followed by 50 gms of D-phenyl alanine, under nitrogen. To it 76 ml HMDS was added at room temperature under stirring. The reaction mass was then heated to reflux temperature and maintained for 3 hours. The reaction mass was then cooled under nitrogen flow to room temperature and then to –5 to 0^{0}C, followed by addition of 100ml of acetonitrile. To it a solution of 60 gms of trans-4-isopropyl cyclohexane carbonyl chloride in 100 ml of acetonitrile were added over a period of 35 to 40 minutes maintaining–4 to 0^{0}C under nitrogen. The reaction mixture was stirred at –5 to 0^{0}C for 3 hours. The reaction mixture was then quenched into ~1.2 L of ice water, stirred for one hour, filtered and washed with water till the pH of the filtrate was 5-5.5. The material was dried in air and then in an oven at 70-75^{0}C for 6-8 hours till the moisture content becomes less than 1%.
Product Weight : 86-88gms [Crude Nateglinide]
Yield : 88-90 %
Purity by HPLC : 98.5-99.5 %
M.P. : 124-128^{0}C

Example- 3

Preparation of Nateglinide form-H from crude Nateglinide
In 2 L capacity multi necked round bottom flask equipped with stirrer, oil bath for heating, condenser, thermometer and dropping funnel was charged 800 ml of cyclohexane followed by 80 gms of crude Nateglinide [product of Example-2] . The reaction mass was heated to reflux temperature. To it 160 ml of ethyl acetate were added dropwise at reflux temperature. Reaction mass was then a clear solution. The reaction mass was then cooled to 45-48^{0}C and maintained at 45-48^{0}C for 16-18 hours. The solid was filtered at 35-40^{0}C, washed with 2x80 ml of cyclohexane , unloaded and dried in oven at 80-85^{0}C. This product was characterized as Nateglinide form–H.
Product Weight : 65-68 gms
Yield :81-85%
Purity by HPLC : >99.7 % Melting Point : 134-139^{0}C

FIELD OF INVENTION :

The present invention relates to commercially viable process for the preparation of Nateglinide and its polymorph form-H.

We claim:

(1) A process for a preparation of nateglinide form H comprising steps:
(a)Reacting trans-4-isopropyl cyclohexane carboxylic acid using oxalyl chloride in an organic solvent at its reflux temperature, to give trans-4-isopropyl cyclohexane carbonyl chloride,
(b) silylating D-phenyl alanine to N,O-bis trimethylsilyl D-phenyl alanine in a solvent at about the reflux temperature of solvent ,
(c) reacting a solution of trans-4-isopropyl cyclohexane carbonyl chloride, with a solution of N,O-bis trimethylsilyl D-phenyl alanine followed by quenching in water to obtain crude nateglinide,
(d) crystallizing the crude nateglinide from a mixture of cyclohexane-ethyl acetate to give nateglinide form-H crystals.

(2) A process for preparation of nateglinide form H, as claimed in claim-1 wherein the solvent used in step (a) is selected from aromatic hydrocarbons such as benzene, toluene, xylene , or mixtures thereof; paraffins such as hexane , heptane, octane, or mixtures thereof; cycloalkanes such as cyclohexane, cyclopentane methyl cyclopentane, methyl cyclohexane or mixtures thereof; halogenated solvents such as dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride or mixtures thereof.

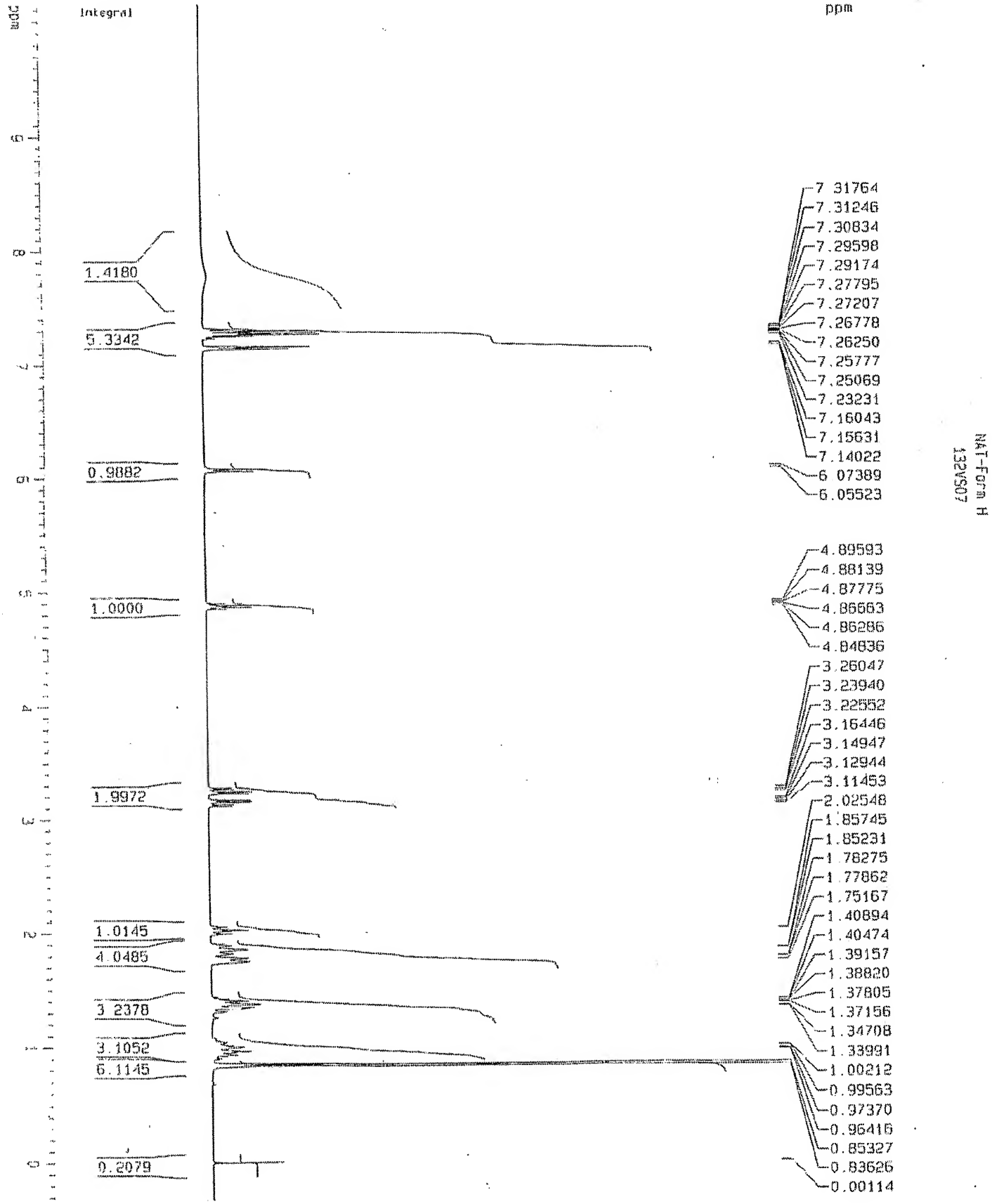
(3) A process for preparation of nateglinide form H, as claimed in claim-2, wherein the solvent is dichloromethane.

(4) A process for preparation of nateglinide form H, as claimed in claim-1 wherein the silylation in step (b) is carried out using a silylating agent such as HMDS, BSU, BSA.

(5) A process for preparation of nateglinide form H, as claimed in claim-1 wherein the solvent used in step (b) is selected from aromatic hydrocarbons such as benzene, toluene, xylene , or mixtures thereof; halogenated solvents such as dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride , or mixtures thereof ; ethers such as THF, dioxane, 2-Methyl THF, dialkyl ether such as diethyl ether, dipropyl ether, dibutyl ether , or mixtures thereof; paraffins such as hexane , heptane, octane or mixtures thereof; cycloalkanes such as cyclohexane, cyclopentane , methyl cyclopentane, methyl cyclohexane or mixtures thereof; nitriles such as acetonitrile, propionitrile , or mixtures thereof.

(6) A process for preparation of nateglinide form H, as claimed in claim-5, wherein the solvent is acetonitrile.

(7) A process for preparation of nateglinide form H, as claimed in claim-1 wherein the reaction of N,O-bis trimethylsilyl D-Phenylalanine with trans-4-isopropyl cyclohexane carbonyl chloride in step (c) is carried out at -10 to 20^0C, preferably at -4 to0^0C .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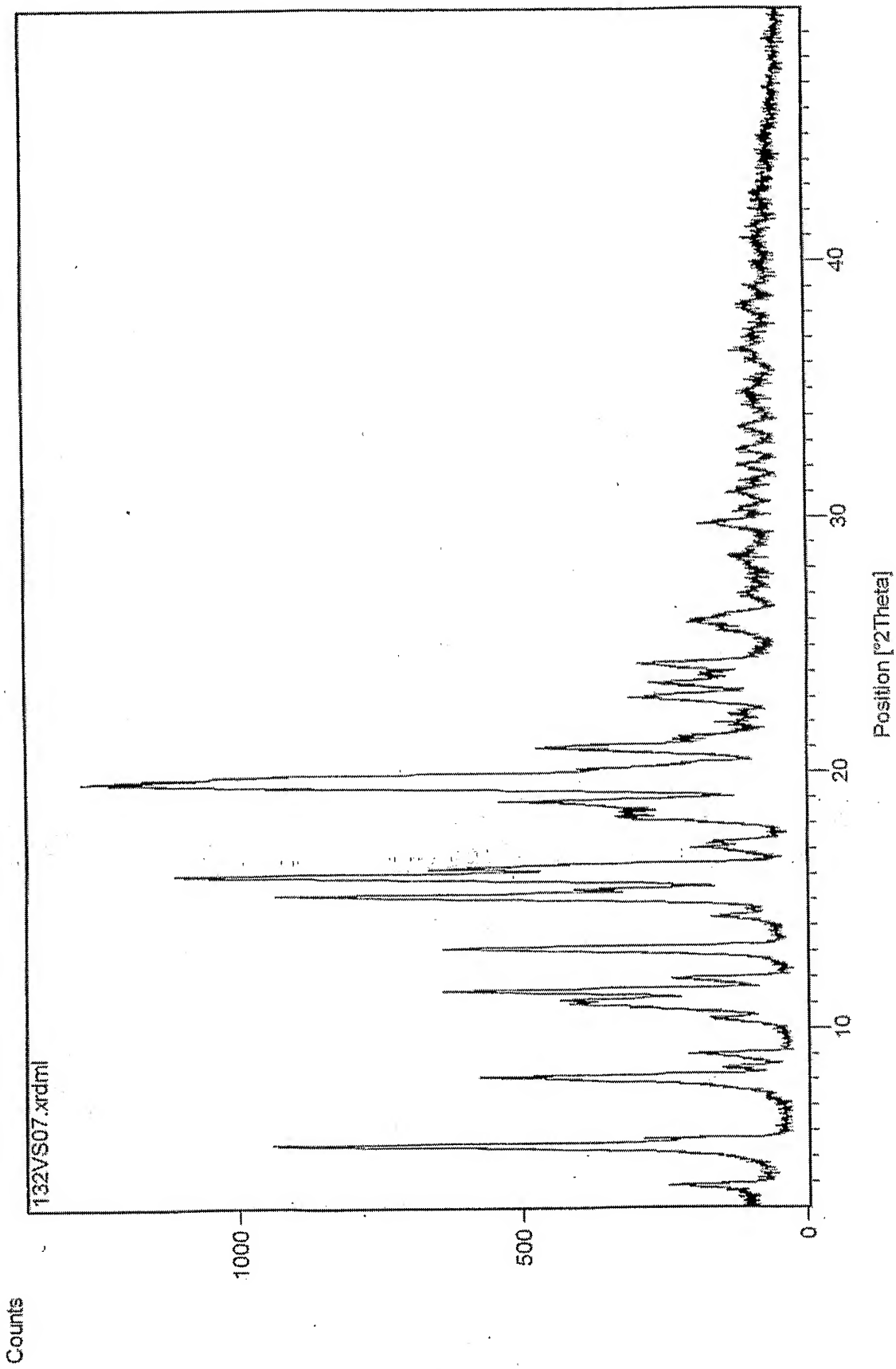
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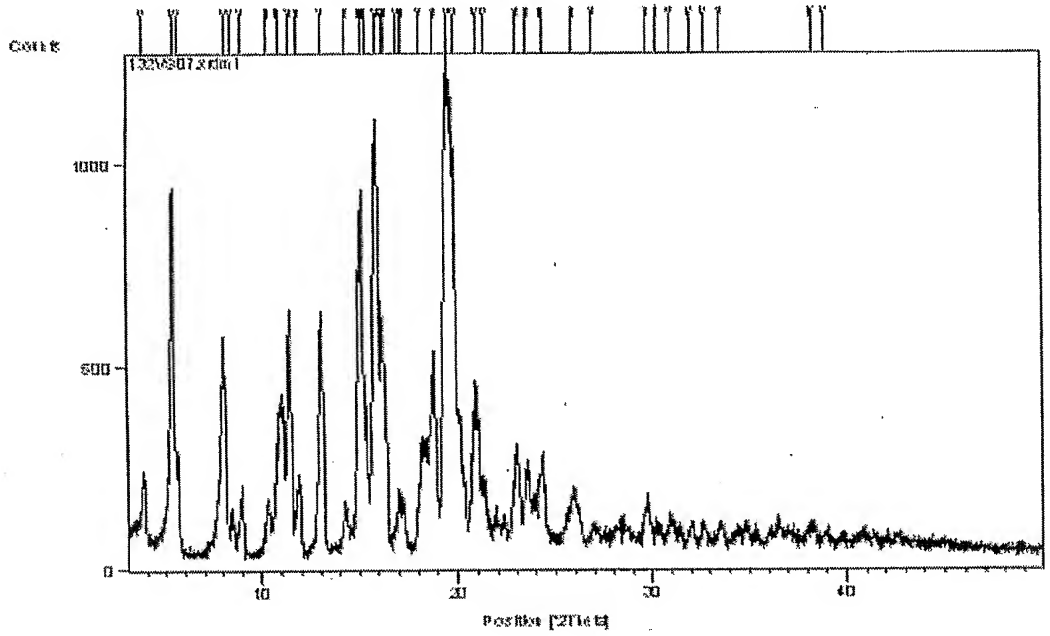
Graphics



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